

Reviewer #1: This is a retrospective study with EMR and ESD of large appendiceal orifice polyps.

- 1) Regarding treatment options for appendiceal orifice polyps. Please indicate whether endoscopic resection or surgical resection should be chosen, and what are the criteria for treatment selection.**

Response:

The following passage has been added to the discussion:

“For evaluation of polyps that may require surgical intervention, the Japanese Gastroenterological Endoscopy Society guidelines for ESD and EMR can be utilized.²⁷ Criteria for surgery may include polyps that meet deep invasion guidelines or have increased concern for malignancy. We suggest that appendiceal orifice polyps that are larger than 2cm should be evaluated on a case to case basis in a multi-disciplinary team for consideration of surgical or endoscopic resection. This decision may vary by institution, depending on the availability of expertise in complex endoscopic resection. Furthermore, patient comorbidities must be considered when pursuing surgical intervention.

Narrow band imaging (NBI), white light endoscopy, and chromoendoscopy are also strategies that can be considered to aid in the detection of high-risk polyps that may harbor advanced neoplasia and require surgical resection rather than endoscopic intervention.²⁸ Based on the NBI International Colorectal Endoscopic Classification (NICE) criteria, type 2 lesions can be addressed with endoscopic resection, while type 3 lesions should be referred for surgical resection.²⁹”

27. Tanaka S, Kashida H, Saito Y, et al. Japan Gastroenterological Endoscopy Society guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc Off J Jpn Gastroenterol Endosc Soc*. 2020;32(2):219-239. doi:10.1111/den.13545

28. Singh R, Owen V, Shonde A, Kaye P, Hawkey C, Ragunath K. White light endoscopy, narrow band imaging and chromoendoscopy with magnification in diagnosing colorectal neoplasia. *World J Gastrointest Endosc*. 2009;1(1):45-50. doi:10.4253/wjge.v1.i1.45

29. Patrun J, Okreša L, Iveković H, Rustemović N. Diagnostic Accuracy of NICE Classification System for Optical Recognition of Predictive Morphology of Colorectal Polyps. *Gastroenterol Res Pract*. 2018;2018:e7531368. doi:10.1155/2018/7531368

- 2) You mentioned that 68% of the cases occupied more than 50% of the appendiceal orifice. Were there any cases that covered the entire appendiceal orifice, i.e., 100% of the cases? Please describe the occupancy rate in more detail.**

Response:

The following passage has been added to the section “polyp appearance” in results:

“Two polyps (11%) covered the entire appendiceal orifice, while five polyps (26%) covered 75-80% of the appendiceal orifice.”

- 3) Only 2 patients (11%) had already undergone appendectomy before endoscopic resection. In most cases, clipping was performed after endoscopic resection, but the risk of appendicitis seems to increase when the wound is sutured with a clip. One patient had appendicitis and underwent appendectomy. Shouldn't clipping be done to prevent appendicitis?**

Response:

The following passage has been added to the “discussion” section:

“Only one patient in our cohort developed appendicitis requiring laparoscopic appendectomy, although the event occurred four months after hybrid EMR/ESD, suggesting that her appendicitis was not related to her polypectomy. In our study, clipping was attempted in all cases, except for one case where a polyp with Paris classification Ip was not invading the appendiceal orifice. This patient did not develop appendicitis or require appendectomy. Nevertheless, clipping should still be attempted to prevent postoperative appendicitis.”

- 4) There are other reports of ESD for appendiceal polyps. Please cite the following paper. Feasibility of endoscopic submucosal dissection for cecal tumors involving the ileocecal valve or appendiceal orifice. Hotta K, et al. J Gastroenterol Hepatol. 2022;37:1517-1524.**

Response:

The following passage has been modified in the “discussion” to include the abovementioned paper:

“There are two studies focusing on the role of ESD in the management of appendiceal polyps. In one Japanese study of 76 polyps (median size 35.5mm) in the cecum adjacent to the appendix (only 29 located at the orifice), en bloc resection and R0 resection were achieved in 94.7% and 92.1% of patients, respectively.²⁰ In another Japanese study of 27 appendiceal orifice polyps (mean size 31.8mm), en bloc resection and R0 resection were achieved in 77.8% and 70.4% of patients, respectively.²¹”

20. Jacob H, Toyonaga T, Ohara Y, et al. Endoscopic submucosal dissection of cecal lesions in proximity to the appendiceal orifice. *Endoscopy*. 2016;48(9):829-836. doi:10.1055/s-0042-110396
21. Hotta K, Osera S, Shinoki K, et al. Feasibility of endoscopic submucosal dissection for cecal tumors involving the ileocecal valve or appendiceal orifice. *J Gastroenterol Hepatol*. 2022;37(8):1517-1524. doi:10.1111/jgh.15872

Reviewer #2: This study evaluated several endoscopic procedures for the resection of large appendiceal polyps, including EMR, ESD, and hybrid EMR/ESD procedures. The authors found these endoscopic techniques were efficacious and safe methods for removal of large appendiceal polyps. This is a very interesting study and a well-written manuscript. But I have a few comments or concerns about this study:

- 1) The authors defined appendiceal large polyps as those greater than 1cm in size. Why did you not use 1.5cm or 2cm as the definition instead?**

Response:

The following passage has been added to the “methods” section:

“The decision to define large appendiceal polyps as $\geq 1\text{cm}$ was based on the following. Multiple prior studies that evaluated endoscopic resection had average appendiceal polyp sizes around 1cm.⁴⁻⁶ Additionally, two other studies had average polyp sizes around 1.5cm.^{7,8} Furthermore, one of these prior studies showed that the odds of polyp recurrence can potentially increase by 3.2 times in polyps $\geq 1\text{cm}$ with conventional polyp removal techniques,⁴ so we wanted to specifically evaluate outcomes in this population.”

4. Hassab TH, Church JM. Appendix orifice polyps: a study of 691 lesions at a single institution. *Int J Colorectal Dis.* 2019;34(4):711-718. doi:10.1007/s00384-019-03251-z
5. Song EM, Yang HJ, Lee HJ, et al. Endoscopic Resection of Cecal Polyps Involving the Appendiceal Orifice: A KASID Multicenter Study. *Dig Dis Sci.* 2017;62(11):3138-3148. doi:10.1007/s10620-017-4760-2
6. Ichkhanian Y, Barawi M, Seoud T, et al. Endoscopic full-thickness resection of polyps involving the appendiceal orifice: a multicenter international experience. *Endoscopy.* 2022;54(1):16-24. doi:10.1055/a-1345-0044
7. Bronzwaer MES, Bastiaansen BAJ, Koens L, Dekker E, Fockens P. Endoscopic full-thickness resection of polyps involving the appendiceal orifice: a prospective observational case study. *Endosc Int Open.* 2018;6(9):E1112-E1119. doi:10.1055/a-0635-0911
8. Binmoeller KF, Hamerski CM, Shah JN, Bhat YM, Kane SD. Underwater EMR of adenomas of the appendiceal orifice (with video). *Gastrointest Endosc.* 2016;83(3):638-642. doi:10.1016/j.gie.2015.08.079

- 2) In the outcomes section, the authors reported “The overall en bloc resection rate was 84%; 100% for the EMR and ESD groups, and 63% for the hybrid EMR/ESD group. The overall R0 resection rate for en bloc resected polyps was 88%. R0 resection rate for the EMR group, ESD group, and hybrid EMR/ESD group was 80%, 100% and 80%, respectively. The curative resection rate was 89%, 80% for the EMR group, 100% for the ESD group, and 88% for the hybrid EMR/ESD group”. There is a question regarding why the curative resection rate was higher than the R0 resection rate, and how the authors defined curative resection. It is**

suggested that authors provide a more well-defined and precise explanation of curative resection.

Response:

The following modifications have been made to the “methods” section for clarification:

“Curative resection was defined as histological complete resection with no risk of lymph node metastasis by histological examination of the resected specimen, according to the Japanese Society for Cancer of the Colon and Rectum guideline criteria.⁷ Patients with piecemeal or R1 resection were considered to not have achieved curative resection.”

The following modifications have been made to the “results” section for clarification:

“The overall curative resection rate was 74%. Curative resection rates were 80% for the EMR group, 100% for the ESD group, and 50% for the hybrid EMR/ESD group.”

- 3) To ensure better clarity and understanding, it is advisable for the authors to provide a more detailed description of their decision-making process for selecting either EMR, ESD, or hybrid ESD techniques for resection of large appendiceal polyps.**

Response:

The following passage has been added to the “methods” section:

“EMR was considered for the resection of pedunculated or sessile appendiceal polyps that were smaller than 1.5cm, did not extend into the appendiceal orifice, and were easily liftable after injecting solution. ESD and hybrid EMR/ESD were considered for polyps that extended into the appendiceal orifice, flat polyps, polyps with underlying scar and previous manipulation, or polyps that did not adequately lift after injecting solution. The overall goal was to achieve en bloc resection.”

- 4) This article had inclusion criteria but no exclusion criteria. I think there should be some exclusion criteria.**

Response:

The following sentence has been added to the “methods” section:

“Exclusion criteria included pediatric patients (less than 18 years of age), patients with polyps < 1cm, and patients with a history of a prior appendiceal orifice polypectomy.”

- 5) The authors did not define procedure time, postoperative bleeding, perforation, and appendicitis in this article, and I think they should have.**

Response:

The following definitions have been added to the “methods” section:

“Procedure time was defined as the time from introduction of the colonoscope into the rectum until withdrawal of the colonoscope. Postoperative bleeding was defined as immediate and long-term bleeding (defined as up to 2 weeks after the procedure) from the polypectomy site that resulted in rectal bleeding or melena. Perforation was defined as transmural injury of the bowel wall resulting in free air in the abdomen. Appendicitis was defined as inflammation of the appendix at any time period after polypectomy.”

- 6) In this passage “En bloc resection rate was defined as resection of the entire polyp in one piece. R0 (complete) resection rate was defined as en bloc resection with negative horizontal and vertical margins. Curative resection rate was defined as histological complete resection with no risk of lymph node metastasis by histological examination of the resected specimen according to the Japanese Society for Cancer of the Colon and Rectum guideline criteria.”⁷, the word "rate" can be removed.**

Response:

The word “rate” has been removed so the passage now reads:

“En bloc resection was defined as resection of the entire polyp in one piece. R0 (complete) resection was defined as en bloc resection with negative horizontal and vertical margins. Curative resection was defined as histological complete resection with no risk of lymph node metastasis by histological examination of the resected specimen, according to the Japanese Society for Cancer of the Colon and Rectum guideline criteria.¹⁰”

- 7) A few mistakes remain in the text, such as “Adverse event such a bleeding and perforation after appendiceal polypectomy has been.....” in discussion section.**

Response:

The manuscript has been checked again for grammatical issues. The abovementioned sentence has been corrected to:

“Adverse events such as bleeding or perforation after appendiceal polypectomy have been...”

Reviewer #3: Thanking authors for bringing the value of using pathfinder / di-lumen for carrying out advanced endoscopic composite procedures. They have touched on the importance of hybrid procedures attentively. However, the numbers in this one centre retrospective study are small, non-RCT, follow up colonoscopy to know the outcomes is missing in 43% of patients, questioning the robustness of this study.

Response: We appreciate Reviewer #3's comments. We acknowledge that the limited number of patients in this single center retrospective study is a limitation. However, this is one of the first studies evaluating EMR and ESD for complex polyps in a Western country. Our results can be used for a future prospective study to evaluate EMR and ESD in complex polyps, as well as in comparison with surgical resection.